REMARKS

The present amendment is being filed with a Request for Continued Examination (RCE). Applicants understand that the amendment and the attached supplemental information disclosure statement satisfy the requirements for submission under 37 C.F.R. § 1.114. Upon entry of the amendment, claims 86-98, 100, and 101 will be pending in the application. Claim 90 remains withdrawn. Claims 93-95 are amended. No new matter has been added by the amendments.

Applicants respectfully request that the Examiner consider the references cited in the Supplemental Information Disclosure Statement, and then return an initialed copy of the form PTO-1449.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has maintained the rejection of claims 93-95 under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter. The Examiner states that "the issue is the lack of antecedent basis in base claims 87-90..." Office Action at page 2. The amendments to claims 93-95 are believe to resolve any issues of improper antecedent basis.

The Examiner further states that "[b]ase claims 87-90 do not specifically point out whether the combination therapy occurs separately, simultaneously, or subsequently." Office Action at page 2. Applicants maintain that the recitation of such order of administration is not required, and the claims, at least as amended, satisfy the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103

I. Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian

The Examiner has maintained the rejection of claims 86-89, 91, 93-97, and 101 under 35 U.S.C. § 103(a) as being unpatentable over Van Zaanen *et al.*, *Br. J. Haematol.* 102:783-790, 1998 ("Van Zaanen") in view of Masellis-Smith *et al.*, *Cancer Res.* 57:930-936, 1997 ("Masellis-Smith") and Lokhorst *et al.*, *Blood* 84:2269-2277, 1994 ("Lokhorst") and U.S. Patent

No. 5,885,786 (1996) ("Cabot") or Alexanian *et al.*, *J. Am. Med. Assoc.* 208:1580-2685, 1969 ("Alexanian").

The Examiner states that Van Zaanen teaches an *in vivo* method for treating multiple myeloma ("MM") comprising administering chimeric monoclonal anti-IL-6 antibodies (cMab) in MM patients. Masellis-Smith *et al.* teaches that the α4ß7 ligand mediates MM blood B cell adhesion. Lokhorst teaches that monoclonal antibodies directed to the α4-integrin (VLA-4) inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. The Examiner further states that Lokhorst *et al.* teach that (i) the intimate cell-cell contact is a prerequisite for IL-6 induction and (ii) the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 inhibited the induction of IL-6 production by LTBMC. The Examiner concludes that one of ordinary skill in the art would have been motivated to substitute the anti-IL-6 antibodies of Van Zaanen with anti-α4 antibodies. Office Action at pages 3-4.

The Examiner also states that Cabot teaches the use of melphalan to treat MM, and Alexanian teaches the use of melphalan in combination with prednisone to treat MM. Office Action at page 3. In view of Cabot and Alexanian, the Examiner states that one of ordinary skill in the art would have been motivated to combine anti-α4 antibodies with a chemotherapeutic agent such as melphalan for the treatment of MM. Office Action at page 4.

Applicants disagree with the Examiner's conclusions. Applicants disagree, in particular, on two main points: (i) that one of ordinary skill in the art would have been motivated to substitute the anti-IL-6 antibodies of Van Zaanen with anti-α4 antibodies; and (ii) that one of ordinary skill in the art would have been motivated to combine anti-α4 antibodies with a chemotherapeutic agent such as melphalan for the treatment of MM. For simplicity, Applicants will address both points in turn below.

(i) One of ordinary skill in the art would not have been motivated to substitute the anti-IL-6 antibodies of Van Zaanen with anti-α4 antibodies.

The Examiner relies on Van Zaanen, Masellis-Smith, and Lokhorst to come to the conclusion that one of ordinary skill in the art would have been motivated to substitute the anti-

IL-6 antibodies of Van Zaanen with anti-α4 antibodies. Applicants disagree with this conclusion.

A Declaration under 37 C.F.R. § 1.132 by inventor Dr. Gregory R. Mundy, submitted herewith, supports Applicants' position. The Declaration of Dr. Mundy at paragraph 4 explains that at the filing date of the pending application, a practitioner of ordinary skill in the field would not, for numerous reasons, have believed that anti-α4 antibodies, such as anti-VLA-4 antibodies, would be interchangeable with anti-IL-6 antibodies to treat MM. First, the art did not teach that the anti-IL-6 antibodies could be used to treat MM. For example, Bataille *et al.* ("Biological Effects of Anti-Interleukin-6 Murine Monoclonal Antibody in Advanced Multiple Myeloma" *Blood* 86:685-691, 1995; cited in the IDS submitted June 21, 2002; courtesy copy enclosed as Exhibit A) taught that anti-IL-6 antibodies were not effective at treating MM. Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. Van Zaanen, which is relied upon by the Examiner, is a phase I dose-escalating study that, at best, shows that anti-IL-6 antibodies are not toxic. None of the patients involved in the study achieved a response according to standard criteria, even though effective IL-6 blocking was detected in 11/12 patients. See Van Zaanen in the abstract and in the discussion at page 787. The teachings of Van Zaanen do not overcome or refute the prior teachings of Bataille *et al.* that anti-IL-6 antibodies are ineffective for the treatment of MM. Evidence that anti-VLA-4 antibodies decreased tumor burden *in vivo* in a mouse model of myeloma bone disease is presented in the pending application (see, e.g., page 66, lines 14-26), and the results of these studies were published in Mori *et al.* ("Anti-α4 integrin antibody suppresses the development of multiple myeloma and associated osteoclastic osteolysis," *Blood* 104:2149-2154, 2004, cited in the IDS submitted herewith). Thus one would conclude that anti-VLA-4 antibodies, but not anti-IL-6 antibodies, would be effective for the treatment of MM.

Masellis-Smith *et al.* teaches that the α4ß7 ligand mediates MM blood B cell adhesion, as evidenced by the ability of the anti-VLA-4 antibody HP2/1 to inhibit adhesion. Although HP2/1 binds the B epitope, which is known to interact with VCAM-1 and fibronectin, Masellis-Smith also found that monoclonal antibodies against VCAM-1 and antibodies against fibronectin did

not affect B cell adhesion (see the abstract and page 933, col. 2 to page 934, col. 1). Thus it was concluded that the HP2/1 antibody inhibits B cell adhesion via a novel ligand. Lokhorst teaches that a monoclonal antibody HP1/7 directed to the A epitope of VLA-4 inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. The anti-VLA-4 antibodies also partially inhibited binding of plasma cells to LTBMC and caused a reduction in IL-6 secretion by LTBMC (see page 2273, col. 2). The Examiner concludes that one of ordinary skill in the art would have been motivated to substitute the anti-IL-6 antibodies of Van Zaanen with anti-α4 antibodies. The Examiner is concluding that Lokhorst teaches that administration of anti-VLA-4 antibodies will cause a decrease in IL-6 levels, and since Van Zaanen *et al.* teaches that IL-6 antibodies can be used for treatment of MM, VLA-4 antibodies can be used for treatment of MM. This logic is flawed at least in view of the statements made by Dr. Mundy in the attached declaration and as described above.

One having ordinary skill in the field of myeloma research would not conclude from the *in vitro* results of Lokhorst and Masellis-Smith that an anti-VLA-4 antibody could be used for the treatment of MM.

(ii) One of ordinary skill in the art would not have been motivated to combine anti-α4 antibodies with a chemotherapeutic agent such as melphalan for the treatment of MM.

The Examiner states that Cabot teaches the use of melphalan to treat MM, and Alexanian teaches the use of melphalan in combination with prednisone to treat MM. Office Action at page 3. In view of Cabot and Alexanian, the Examiner states that one of ordinary skill in the art would have been motivated to combine anti-α4 antibodies with a chemotherapeutic agent such as melphalan for the treatment of MM. Office Action at page 4. Applicants disagree.

There is no support in the cited art that anti-VLA-4 antibodies can be substituted for prednisone in a combination therapy with melphalan to treat MM, at least because anti-VLA-4 antibodies and prednisone have dramatically different structures and dramatically different biological effects. Anti-VLA-4 kills myeloma cells by interfering with myeloma cell attachment to host bone marrow cells (see specification, *e.g.*, at page 65, lines 1-7, and 18-29; page 66 line 8 to page 67 line 5; and page 70, lines 22-29). Prednisone kills cancer cells regardless of whether or not they are interacting with other cells. Thus whether prednisone and melphalan in

combination can be used to treat MM is irrelevant as to whether a combination of an anti-VLA-4 antibody and melphalan can be used to treat MM, even in view of Van Zaanen, Masellis-Smith, and Lokhorst.

These points are emphasized in paragraph 6 of the attached Declaration by Dr. Mundy, which states that at the filing date of the pending application, a practitioner of ordinary skill in this field would not have believed that anti-VLA-4 antibodies could substitute for the prednisone taught by Alexanian *et al.* in a combination therapy with melphalan for the treatment of MM. One of ordinary skill in the art would not make this substitution at least because anti-VLA4 antibodies and prednisone are different types of molecules having different therapeutic targets, and therefore different therapeutic effects. Anti-VLA4 antibodies are very specific targeting molecules that kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. Prednisone is a broad spectrum agent which kills cancer cells regardless of whether or not they are interacting with other cells. Thus whether prednisone and melphalan in combination can be used to treat MM (as described in Alexanian) is irrelevant insofar as predicting whether a combination of an anti-VLA-4 antibody and melphalan can be used to treat MM. Even in view of Van Zaanen, Masellis-Smith, and Lokhorst, a therapeutic effect of a combination therapy of prednisone and melphalan for treatment of MM is not predictive of a therapeutic effect of a combination therapy of anti-VLA-4 antibodies and melphalan.

At page 4 of the Office Action, the Examiner states that "the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07" The Examiner further cites In re Kerkhoven, 626 F.2d 846, 850 (CCPA 1980), as standing for the proposition that "it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art." Office Action at page 4. The Examiner's argument is flawed, however, because both components recited in claim 86 ((i) an anti-VLA-4 antibody or antigen-binding fragment thereof, and (ii) a chemotherapeutic agent) are not taught in the prior

art as therapies for MM. Therefore, the idea of combining the two components for treatment of MM does not flow logically from their having been individually taught in the prior art.

To summarize the arguments presented in points (i) and (ii) above, VLA-4 and IL-6 have distinct functions in the progression of MM. This is evidenced by the ability of anti-VLA-4 antibodies to decrease tumor burden *in vivo* in models of myeloma bone disease (see the specification at page 66 lines 14-26), and the inability of anti-IL-6 antibodies to treat MM in clinical studies (see Van Zaanen and Bataille *et al.* (1995)). Thus, while VLA-4 can reduce the levels of IL-6 *in vitro* (Lokhorst *et al.*), this effect is not relevant to the anti-tumor effects of anti-VLA-4 antibodies observed *in vivo*. Furthermore, a combination of anti-VLA-4 and melphalan for the treatment of MM is not obvious because (i) anti-VLA-4 antibodies affect different target molecules than prednisone, and will therefore have a different therapeutic effect when combined with melphalan than when the latter is combined with prednisone, and (ii) anti-VLA-4 was not known to be useful for treatment of MM prior to Applicants' filing date, and thus it would not have been obvious to combine these antibodies with any other chemotherapeutic agent for treatment of MM.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must by some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teaching. Second, there must be a reasonable expectation of success, and third, the prior art reference must teach or suggest all the claim limitations. MPEP 2142, citing In re Vaeck, 947 F.2d 488 (Fed. Circ. 1991). As described above, in view of the references cited by the Examiner, one of skill in the art of cancer therapies would not be motivated to substitute an anti-VLA-4 antibody for an anti-IL-6 antibody for the treatment of MM and further would not be motivated to combine an anti-VLA-4 antibody with a chemotherapeutic agent for the treatment of MM. Thus the Examiner has not established a *prima facie* case of obviousness.

In view of the foregoing, claims 86-89, 91, 93-97, and 101 are not unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst, and Cabot or Alexanian.

The Examiner also alleges that U.S. Patent No. 6,692,742 ("Nakamura") reports "the same claimed unexpected surprising results" described by Applicants. Office Action at page 6. Nakamura describes a combination of melphalan and an anti-IL-6 receptor antibody to treat MM. Applicants disagree that Nakamura demonstrates the "same" surprising results. As provided in paragraph 7 of the Declaration by Dr. Mundy, evidence that an anti-IL-6 receptor antibody in combination with melphalan can treat MM is irrelevant insofar as predicting whether a combination of an anti-VLA-4 antibody and melphalan can be used to treat MM. An anti-IL6 receptor antibody will disrupt a multitude of pathways, as this receptor interacts with two classes of ligands called gp130 ligands and gp80 ligands. See Schwabe *et al., J. Biol. Chem.* 269:7201-7209, 1984. Thus in view of evidence that a combination of anti-IL-6 receptor antibodies and melphalan can treat MM, one of skill in the art would not conclude that an anti-VLA-4 antibody (which disrupts a very different interaction) in combination with a chemotherapeutic agent would also be effective for the treatment of MM. As described above, studies described in the prior art indicate that anti-VLA-4 antibodies kill myeloma cells through a mechanism that is independent of IL-6.

For a description of the structure and function of the IL-6 receptor, see, *e.g.*, Schwabe *et al., J. Biol. Chem.* 269:7201-7209, 1984; and Chevalier *et al., J. Biol. Chem.* 271:14764-14772, 1996, both cited in the attached IDS.

Unexpected results. In the Reply to Office Action filed May 16, 2005 ("the May 16th Reply"), Applicants presented evidence of surprising results following treatment of MM with a combination therapy including anti-VLA-4 antibodies and melphalan. In response, the Examiner states that "Applicant's reliance on unexpected superior results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997). The issue is whether the properties differ to such an extent that the difference is really unexpected." Office Action at page 5. The Examiner seems to conclude that Applicants' results were not really unexpected because Van Zaanen teaches a method for treating multiple myeloma by administering anti-IL-6 antibodies, Cabot teaches treatment of MM with melphalan, and Alexanian teaches that treatment of MM with a combination of melphalan and prednisone has a higher response rate than treatment with melphalan alone. Office Action at

page 6. As stated above, Van Zaanen, at best, only teaches that anti-IL-6 antibodies are not toxic, and the teachings of Alexanian do not suggest treatment of MM with a combination of a chemotherapeutic agent and anti-VLA-4 antibodies at least because prednisone and anti-VLA-4 are very different molecules, and therefore are expected to have different therapeutic effects *in vivo*.

In In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995), the court stated: "Consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results." In the May 16th Reply, Applicants' noted the synergistic results described at page 72, lines 6-18, and Figure 8, which describes a significant decrease in serum IgG2 levels (an indicator of decreased tumor burden) in mice treated with a combination of anti-VLA-4 antibodies and melphalan. This result was surprising in view of the observation that no significant decrease was observed following treatment with either agent alone. The Examiner responds by reminding Applicants of the teachings of Van Zaanen, Cabot and Alexanian and concludes that "one of ordinary skill in the art at the time of the invention was made would expect the combination therapy of anti-VLA-4 antibodies and melphalan...to possess the expected beneficial result..." Office Action at pages 5-6. Applicants disagree. As described above, one of skill in the art would not read these references to suggest the surprisingly beneficial result observed by Applicants.

Dr. Mundy states at paragraph 8 of the Declaration that a combination of melphalan and anti-VLA-4 antibody was observed to have a synergistic effect on the treatment of MM (see the specification at page 72, lines 6-20). As shown in Figure 8 of the specification, treatment with antibody alone (200 μg initial dose for the first week, followed by a maintenance dose of 100 μg) reduced IgG2b levels from about 2.7 mg/mL to about 2 mg/mL, and treatment with melphalan alone (100 μg) similarly reduced IgG2b levels from about 2.7 mg/mL to about 2 mg/mL. However, treatment with the combination of antibodies and melphalan resulted in a much more significant decrease in IgG2b levels (from about 2.7 mg/mL to about 0.3 mg/mL). The effect of IgG2b levels is indicative of a decrease in tumor burden. The synergistic result observed with the combination of melphalan and anti-VLA-4 was unexpected and surprising because there was

no reason to expect such a dramatic improvement in view of the mild effects observed with either melphalan or antibody alone.

Applicants do not concede that the Examiner has established a *prima facie* case of obviousness. However, even if this was the case, the court in In re Soni, at 751, stated that "when an applicant demonstrates *substantially* improved results...and *states* that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." (Emphasis in original). Indeed, the specification describes substantially improved results when anti-VLA-4 antibodies and melphalan were combined. This result was surprising and unexpected as stated explicitly by Dr. Mundy in the attached Declaration. Applicants therefore maintain that the claims are not obvious in view of the cited references.

The Examiner seems to particularly rely on the teaching of Alexanian that a method of treating multiple myeloma using a combination therapy with melphalan and prednisone had a higher response rate in comparison with melphalan alone. Because anti-VLA-4 antibodies have a completely different structure and biological target than prednisone, one would not draw any predictions of a treatment with an anti-VLA-4/melphalan combination from the outcome of treatment with a combination of prednisone and melphalan.

The application of Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997) to the present case is also not appropriate as the facts are quite distinct. In Richardson-Vicks, a combination of ibuprofen and pseudoephedrine combined in single form was found to be obvious in view of prior art products which combined analgesics such as acetaminophen and aspirin with pseudoephedrine in single unit dose. The court found the combination to be obvious at least because ibuprofen was a known analgesic that was interchangeable with either aspirin or acetaminophen. Richardson-Vicks at 1187. In contrast, Applicants' anti-VLA-4 antibodies are a completely different molecule, structurally and functionally, than the prednisone of Alexanian *et al.* and it is not at all obvious to substitute one for the other in a therapeutic composition. In addition, the ibuprofen and pseudoephedrine of Richardson-Vicks had been previously prescribed in separate doses. Id. The court also found that the likelihood that ibuprofen would be approved as an over-the-counter medication created a strong motivation to combine the claimed ingredients in a single dose. Id. Unlike in Richardson-Vicks, there is no teaching in the prior art that anti-VLA-4 antibodies and melphalan have previously been prescribed in separate

doses, and there is no motivation to combine the anti-VLA-4 antibodies with a chemotherapeutic agent for the treatment of MM. The prior art cited by the Examiner is distinguished from the prior art teachings relied upon in Richardson-Vicks.

The court in Richardson-Vicks also noted that evidence of unexpected results must be considered in evaluating the obviousness of a claimed invention. Id. at 1186. For the reasons described above distinguishing Applicants' facts from those in Richardson-Vicks, Applicants maintain that the evidence of surprising synergistic results observed with treatment using a combination of anti-VLA-4 antibodies and melphalan, particularly as emphasized in the Declaration by Dr. Mundy, is sufficient to overcome the prior art references cited by the Examiner.

In view of the foregoing, Applicants respectfully request that the rejection of claims 86-89, 91, 93-97, and 101 under 35 U.S.C. § 103(a) be withdrawn.

The Examiner has maintained the rejection of claim 92 under 35 U.S.C. § 103(a) as being unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian and further in view of Owens *et al.* (1994). The Examiner has also maintained the rejection of claims 98 and 100 under 35 U.S.C. § 103(a) as being unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian and further in view of U.S. Patent No. 5,840,299 (Bendig). The teachings of Owens and Bendig do not make up for the deficiencies of Van Zaanen, Masellis-Smith, Lokhorst, Cabot, and Alexanian and are cited solely for their reference to modified antibodies (*e.g.*, chimeric and humanized antibodies), and a humanized anti-VLA-4 antibody, respectively. Applicants therefore respectfully request that the rejection of claims 92, 98 and 100 be withdrawn.

II. Lee in view of Kamata and Cabot or Alexanian

The Examiner has maintained the rejection of claims 86-89, 91, 93-97, and 101 under 35 USC 103(a) as being unpatentable over US Patent No. 6,495,525 ("Lee") in view of Kamata *et al.* and U.S. Patent No. 5,885,786 ("Cabot") or Alexanian *et al.*, *J. Am. Med.Assoc.* 208:1580-2685, 1969 ("Alexanian").

Lee discloses the use of a small molecule VLA-4 inhibitor (oMePUPA-v) to treat animal models of pulmonary inflammation and delayed type hypersensitivity. Lee suggests that the small molecule inhibitor could also be used to treat "VLA-4 mediated cell adhesion and pathologies associated with that adhesion, such as inflammation and immune reactions" and lists 20 specific disorders within that class. Kamata discloses various anti-VLA-4 antibodies and their epitopes but does not teach or suggest the use of anti-VLA-4 antibodies for the treatment of MM. Cabot teaches the use of melphalan to treat MM, and Alexanian teaches the use of melphalan in combination with prednisone to treat MM.

In the May 16th Reply, Applicants presented arguments describing why one having ordinary skill in the art would not be motivated to substitute an anti-VLA-4 antibody for the small molecule of Lee *et al.* for treatment of MM. These arguments included: (i) antibodies are much larger than the small molecule disclosed in Lee *et al.* and thus will affect their targets differently thereby resulting in different effects *in vivo*; (ii) an antibody-based therapy, unlike a small-molecule drug therapy, would be expected to implicate aspects of the immune response and thus elicit different effects *in vivo*; (iii) anti-VLA-4 antibodies have a different specificity than the small molecule of Lee *et al.*; (iv) a skilled artisan would not be motivated to use an antibody therapeutic for treatment of MM in view of the data presented in Lee *et al.*, which demonstrated use of a small molecule to treat inflammation; and (v) Example 3 in Lee *et al.* provides evidence that the small molecule and anti-VLA-4 are not equivalent.

In response to Applicants' argument that a small molecule is not simply interchangeable with an anti-α4 antibody, the Examiner describes the results in example 3 at col. 22, lines 28-52, where it is described that an anti-VLA-4 antibody inhibited swelling in a mouse model of inflammation, while the small molecule oMePUPA-V had no effect. The Examiner concludes that "the '525 patent teaches anti-VLA-4 antibody...mimic the function of oMePUPA-V." Office Action at page 9. On the contrary, this is evidence that the anti-VLA-4 antibody and the oMePUPA-V molecule are <u>not</u> interchangeable and in fact have different therapeutic effects *in vivo*. The Examiner also concludes that "the ordinary skilled artisan would be motivated to substitute an antibody disclosed in Kamata for the small molecule drug" (Office Action at page 9) and further that in view of the teachings of Lee, it is understood that the "antibody would always work, irrespective of whether the small organic molecule inhibits the delayed type

hypersensitivity or not." Office Action at page 10. Applicants submit that the Examiner is drawing overly grand conclusions from the teachings of Lee. Applicants further maintain that one of ordinary skill in the art would not conclude that an antibody effective for reducing inflammation in the hypersensitivity model would be effective for the treatment of multiple myeloma. An effect on the one indication (inflammation), is not predictive of an effect on the other (MM).

In response to Applicants' argument that the antibodies and small molecules are vastly different structures and will effect their targets differently, the Examiner notes that Lee teaches anti-VLA-4 antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions *in vitro* and *in vivo*. Office Action at page 9. The Examiner is referring to a sentence in the background section at col. 1, lines 58-60. The Examiner is ignoring the remaining disclosure in the background section which states that "there remains a need for low molecular weight, specific inhibitors of VLA-4 dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties..." Lee *et al.* at col. 2, lines 54-58. Thus Lee *et al.* teaches that small molecule inhibitors would not be equivalent to antibody inhibitors, and at least in some ways would exhibit "improved pharmacokinetic and pharmacodynamic properties." A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

The Examiner also states that "obviousness does not require absolute predictability, however, at least some degree of predictability is required." Office Action at page 9. The Examiner further cites In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976), as standing for the proposition that evidence showing no reasonable expectation of success may support a conclusion of nonobviousness. The court also held in this case that evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. See also MPEP 2143.02. In view of the attached Declaration by Dr. Mundy, Applicants maintain that there would not have been any expectation of success to treat MM with anti-VLA-4 antibodies in view of the teachings of Lee *et al.* even in combination with the teachings of Kamata, Cabot and Alexanian.

In the May 16th Reply, Applicants noted that an antibody based therapeutic would be expected to implicate aspects of the immune response in its effect. May 16th Reply at page 17. The binding of Fc receptors by the Fc domain of an antibody molecule provides signals that activate and recruit immune and inflammatory cells, or, alternatively, that send inhibitory signals that downregulate immunity. The Examiner responded that the pending claims recite antigen-binding fragments that do not require the Fc domain. Office Action at page 9. Recitation of antigen-binding fragments in the claims does not eliminate the fact that the claims also encompass anti-VLA-4 antibodies that do include the Fc domain. Applicants' point is still valid to show why it would not be obvious to use an anti-VLA-4 antibody in exchange for the small molecule described in Lee *et al.*

Applicants also reminded the Examiner that the anti-VLA-4 antibodies recited in the claims can bind α4ß1 as well as α4ß7. May 16th Reply at page 17. The Examiner responded by stating that VLA-4 encompasses only α4ß1. Office Action at page 9. While it is true that VLA-4 encompasses α4ß1, an anti-VLA-4 antibody encompasses antibodies that can bind α4ß1 as well as α4ß7. The specification describes anti-VLA-4 antibodies, *e.g.*, at page 36, line 27, through page 37, line 12. The specification at page 37, lines 4-8 states: "Anti-VLA-4 antibodies that will recognize the VLA-4 α4 chain epitopes involved in binding to VCAM-1 and fibronectin ligands...are preferred." The specification also recites HP2/1 (see page 37) and PS2 (see the examples, *e.g.*, at page 66) as exemplary anti-VLA-4 antibodies and which are known to bind α4ß1 as well as α4ß7. See Kalamata *et al.* 1995, in the abstract.

In the May 16th Reply, Applicants also submitted that there is no motivation in Lee *et al.* to select multiple myeloma from the long list of disorders in this references for treatment with an antibody. May 16th Reply at page 17. The Examiner responds that the Lee patent is presumed valid and the claims are presumed enabled. Office Action at page 9. While Applicants concede that the teachings of Lee would motivate one to treat of MM with a small molecule, Applicants maintain that there is no motivation to treat MM with an antibody.

Applicants also submit herewith as Exhibit B a Declaration by Dr. Blake Pepinsky filed in a related U.S. application, U.S.S.N. 09/805,840. Applicants' application is a grandchild application of U.S.S.N. 09/805,840. The Declaration by Dr. Pepinsky provides evidence from the viewpoint of an expert in the field of antibody therapeutics and small molecule therapeutics

of why a practitioner of ordinary skill in this field would not, for numerous reasons, have believed that oMePUPA-V would be interchangeable with anti-α4 integrin antibodies to treat multiple myeloma. The comments of Dr. Pepinsky reflect the attorney arguments already of record. Applicants respectfully request that the Examiner consider the comments of this declaration in the reconsideration of the outstanding rejection.

In view of the foregoing, Applicants maintain that claims 86-89, 91, 93-97, and 101 are not unpatentable over Lee in view of Kamata, and Cabot or Alexanian. Applicants therefore respectfully request that the rejection of these claims under 35 U.S.C. § 103(a) be withdrawn.

The Examiner has maintained the rejection of claim 92 under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of Kamata and Cabot or Alexanian and further in view of Owens *et al.* (1994). The Examiner has also maintained the rejection of claims 98 and 100 under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of Kamata and Cabot or Alexanian and further in view of U.S. Patent No. 5,840,299 (Bendig). The teachings of Owens and Bendig do not make up for the deficiencies of Lee, Kamata, Cabot and Alexanian and are cited solely for their reference to modified antibodies (*e.g.*, chimeric and humanized antibodies), and a humanized anti-VLA-4 antibody, respectively. Applicants therefore respectfully request that the rejection of claims 92, 98 and 100 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants contend that the present claims are in condition for allowance, which action is respectfully requested. Should the Examiner maintain any of the present grounds for rejection, the favor of a telephone call to the undersigned is respectfully requested.

Enclosed is a $2160 check to cover the fee for a five-month Petition for Extension of Time and a $790 check for the RCE fee required under 37 C.F.R. §1.17(e). Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 10274-063001.

Respectfully submitted,

Date: September 11, 2006

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